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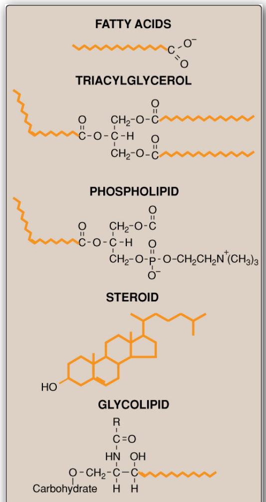
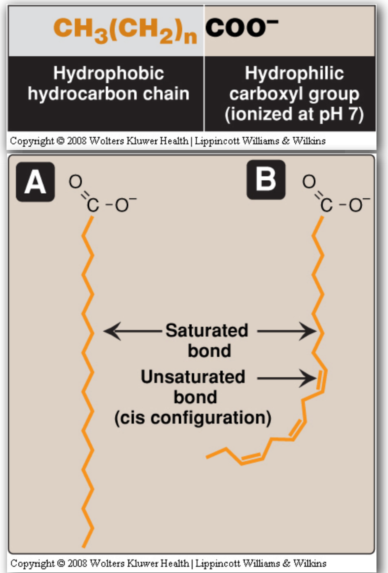
# Lipids

1. Water Insoluble, heterogeneous molecules.
   A) Functions
      a) compartmentalize cellular components and biochemical pathways: membranes
      b) storage of metabolic energy
      c) coenzymes
      d) signaling molecules and effectors
   B) Hydrophobic, lipophilic
   C) Major factor in obesity, diabetes, atherosclerosis



## Fatty Acid Structure

1. Vary in total number of carbons in the acyl chain.
2. Can contain double bonds (normally found in the cis configuration), but are usually unbranched.
3. Always amphipathic due to invariant carbonyl end.






## “Δ” nomenclature locates double bonds: counting from the carbonyl end

Oleic Acid
cis-.delta.9-Octadecenoic acid
cis-Delta(9)-octadecenoic acid
cis-delta(sup 9)-Octadecenoic acid
<i>cis</i>-9-Octadecenoic Acid
Oleic acid (8CI)
(9Z)-Octadecenoic acid
9-Octadecenoic acid, (Z)-
Oleic acid-9,10-t
9-Octadecenoic acid (9Z)-
nchembio.103-comp16
e.g. cis-Δ(9)-octadecenoic acid
9-cis-Octadecenoic acid
(Z)-Octadec-9-enoic acid
Emersol 220 white oleic acid
{Oleic Acid}
9,10-Octadecenoic acid
9-Octadecenoic acid (9Z)- (9CI)
cis-9-Octadecenoic-9,10-3H2 acid
cis-.delta.(sup 9)-Octadecenoic acid
9-Octadecenoic acid (Z)-, sulfurized
9-Octadecenoic acid (9Z)-, sulfurized
9-Octadecenoic-9,10-t2 acid, (Z)-
4-02-00-01641 (Beilstein Handbook Reference)
9-Octadecenoic-9,10-t2 acid, (9Z)- (9CI)

Tuesday, September 30, 2008

## "Δ" nomenclature locates dbl bonds: counting from the carbonyl end

1. cis-Δ(9,12,15)-octadecatrienoic acid
2. n-Hexadecanoic acid
3. cis-Δ(9)-octadecenoic acid
4. cis-Δ(9,12)-octadecadienoic acid

Fatty acids with chain lengths of four to ten carbons are found in significant quantities in milk.

Structural lipids and triacylglycerols contain primarily fatty acids of at least sixteen carbons.

| COMMON NAME | STRUCTURE |
|---|---|
| Formic acid | 1 |
| Acetic acid | 2:0 |
| Propionic acid | 3:0 |
| Butyric acid | 4:0 |
| Capric acid | 10:0 |
| Palmitic acid | 16:0 |
| Palmitoleic acid | 16:1(9) |
| Stearic acid | 18:0 |
| Oleic acid | 18:1(9) |
| Linoleic acid | 18:2(9,12) |
| α-Linolenic acid | 18:3(9,12,15) |
| Arachidonic acid | 20:4(5, 8,11,14) |
| Lignoceric acid | 24:0 |
| Nervonic acid | 24:1(15) |

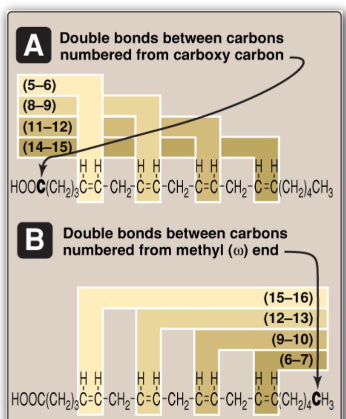
Precursor of prostaglandins

Essential fatty acids

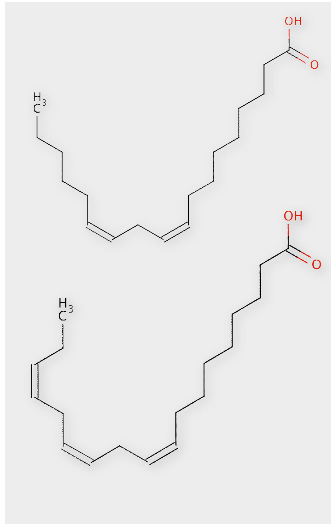


## "ω" [omega] nomenclature marks the first dbl bond from the opposite, or, methyl end

1. **ω** (omega) carbon numbering – **terminal methyl group is always the omega carbon**. Begin counting at omega carbon (#1); most common are ω-6 or N-6 or n-6 (linoleic) and ω-3 (N-3; n-3) (linolenic) fatty acids. These two are **"essential" fatty acids**.

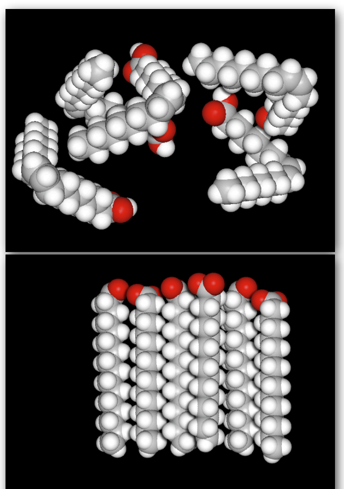


Examples of essential ω-3 (linolenic acid), and an ω-6 (linoleic acid) fatty acids



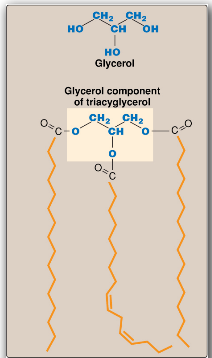

## Saturated Fatty Acids have higher melting points

1. An example of this includes Olive oil versus Crisco shortening.
2. Degree of saturation of fatty acids greatly affects membrane behavior.



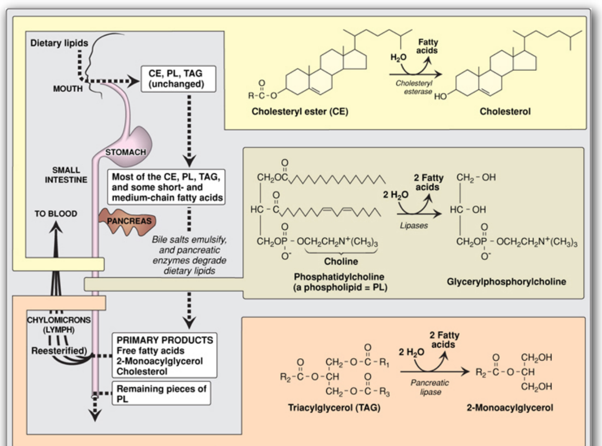
# Triacylglycerols (TAG's) are the storage form of fatty acids

1. The majority of our fatty acid intake is from our diet
2. When cellular energy is plentiful, fatty acids can be synthesized de novo
3. The acyl chain on carbon 1 of a TAG is usually saturated, that on carbon 2 is often unsaturated, and that on carbon 3 can by either.

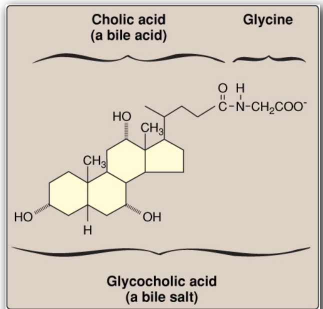




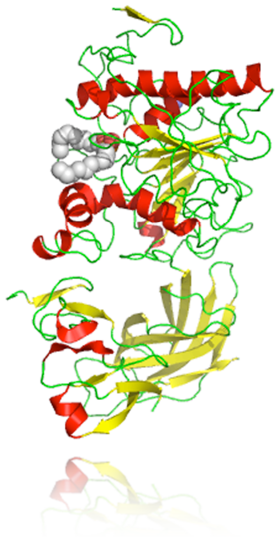

# Fats are broken down to forms that can passage into intestinal mucosal cells



## The critical players for the uptake of fats from the diet are: pancreatic lipase and bile salts

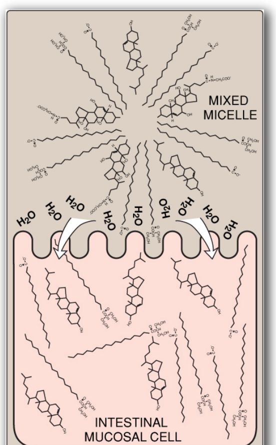




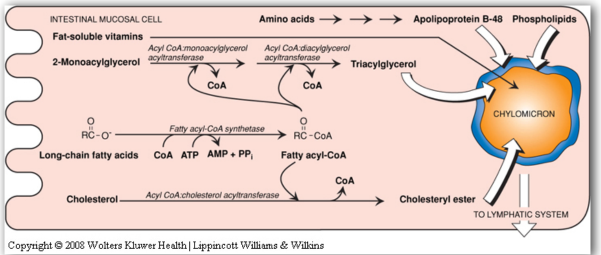



## Digested fats form mixed micelles in the intestinal lumen

1. Fatty acids, monoacyglycerol and cholesterol can be absorbed by intestinal mucosal cells.
2. After absorption, triacylglycerols are re-formed and cholesterol re-esterified.
3. These [very hydrophobic] compounds are packaged by apolipoproteins into chylomicrons for transport throughout the body via lymphatic and, subsequently, blood stream.
4. Short and medium chain fatty acids can be directly absorbed by intestinal mucosal cells.



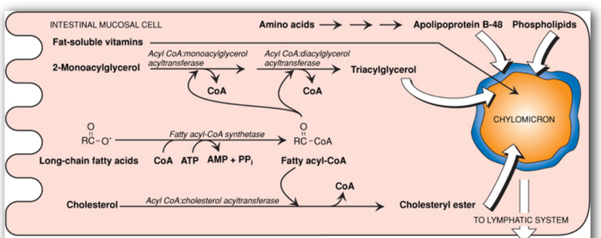
## Resynthesis of triacylglycerides and cholesteryl esters at the ER of intestinal mucosal cells






1. Fatty acids are activated by fatty **acyl CoA synthetase** [requires ATP].
2. **Triacylglycerol synthase** re-joins 2-monoacylglycerol with two fatty acyl CoA
3. Cholesterol is re-esterified with fatty acyl CoA by Acyl CoA cholesterol acyltransferase

## Chylomicrons transport TAG's and Cholesterol-esters to peripheral tissues



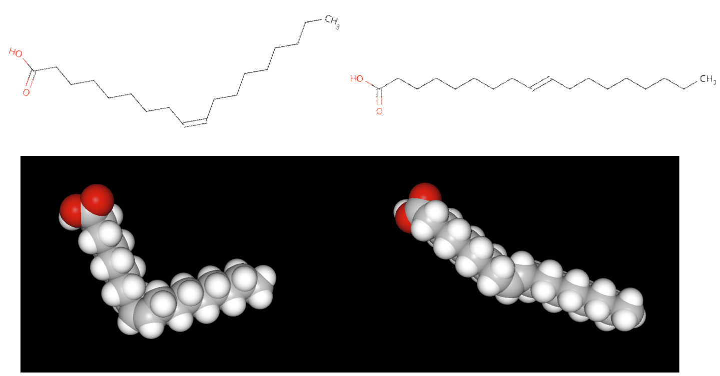



1. Mature Chylomicrons contain TAG's, cholesterol, cholesterol esters, phospholipids and apoliporotein B-48.
2. The apolipoprotein stabilizes the particle and increases its solubility. It also prevents multiple particles from coalescing into a large mass.

## TAG's in chylomicrons are broken down primarily in the capillaries of skeletal muscle and adipose tissue

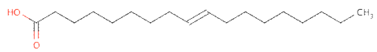
1. **Lipoprotein lipase** degrades TAG's into free fatty acids and glycerol
2. Free fatty acids can be absorbed by neighboring cells or transported to other sites by the carrier protein, albumin.
3. Glycerol that is released from triacylglycerol is used **primarily by the liver** to produce **glycerol 3-phosphate** which can by utilized by glycolysis or gluconeogenesis

## Unsaturated bonds are typically in *cis* configuration

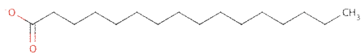


Oleic acid    Elaidic acid

## *trans* fatty acids can also be incorporated into TAG's and phospholipids

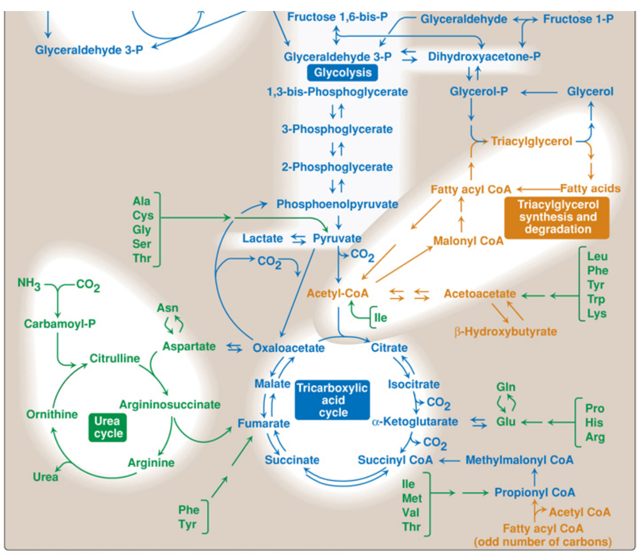
Elaidic acid 


versus

Palmitic acid 

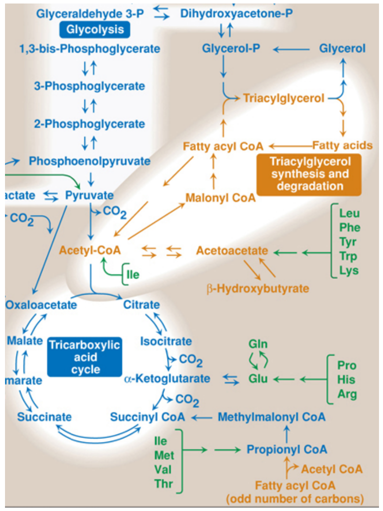

Why are *trans* fatty acids unhealthy?

1. epidemiological studies
2. biochemical studies



## Fatty acid degradation provides metabolic energy in several ways

1. Via breakdown of acyl chains into a number of Acetyl-CoA molecules.
2. Via recovery of Glycerol-6-phosphate from triacylglycerols.
3. During starvation, hepatocytes divert Acetyl-CoA from the TCA cycle (which is driving gluconeogenesis) towards production of Ketone Bodies (primarily Acetoacetate).




## FATTY ACID BIOSYNTHESIS

1. Sites - major (liver, lactating mammary gland) and minor (adipose tissue, kidney)
2. Precursors and cofactors – acetyl CoA, ATP, NADPH, $CO_2$
3. Main site of synthesis is in the cytoplasm
4. Cytoplasmic acetyl CoA is from transported mitochondrial acetyl CoA
   1. Citrate shuttle transports acetyl CoA from mitochondria and to cytoplasm (Fig. 16.6) - *mitochondrial citrate synthase* (OAA + Acetyl CoA) → citrate → cytoplasm → cytoplasmic citrate lyase (OAA + Acetyl CoA)
5. acetyl CoA is precursor for fatty acid synthesis; energy charge (ATP levels) must be high in the cell

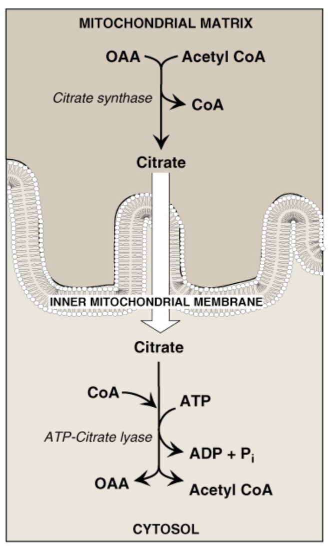
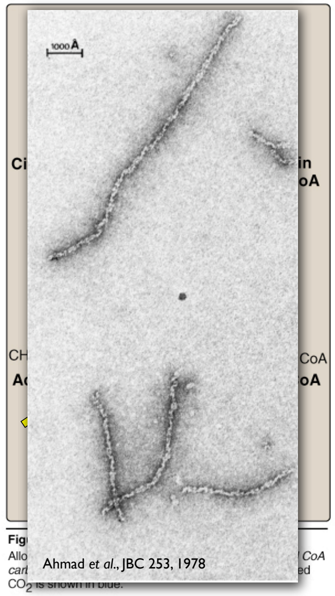



**Figure 16.6**
Production of cytosolic acetyl CoA.

6. Carboxylation/decarboxylation – provides energy and mechanism for synthesis *(Fig. 16.7)* – *acetyl CoA carboxylase* (covalently bound biotin); ATP; $CO_2$; product is malonyl CoA (3 carbons)

7. Regulation of *acetyl CoA carboxylase* (rate-limiting, committed enzyme)

a) short term - polymerization of dimer (protomer) is stimulated by citrate; inhibited by malonyl CoA and palmitoyl CoA *(Fig. 16.7)*




b) phosphorylation – glucagon and epinephrine stimulate phosphorylation = inactive; high insulin and carbohydrates promote dephosphorylation = active (Fig. 16.8)

c) long term - enzyme levels; increased by high carbohydrate, low fat diet (high citrate activates); inhibited by low carbohydrate, high fat diet. Same is true for fatty acid synthase

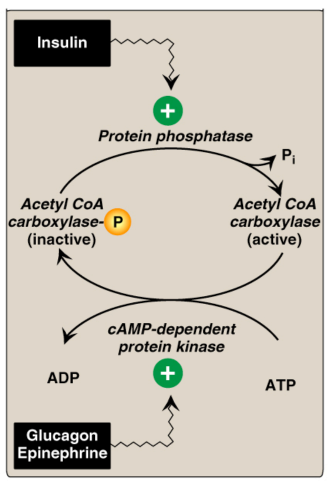
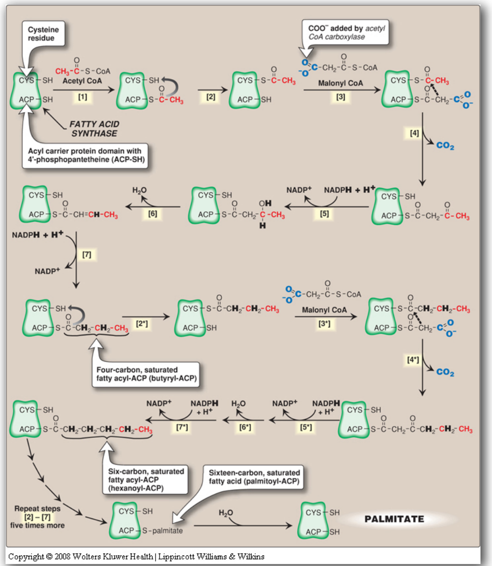



**Figure 16.8**
Hormone-mediated, covalent regulation of *acetyl CoA carboxylase*.

Tuesday, September 30, 2008

# Fatty acid synthase

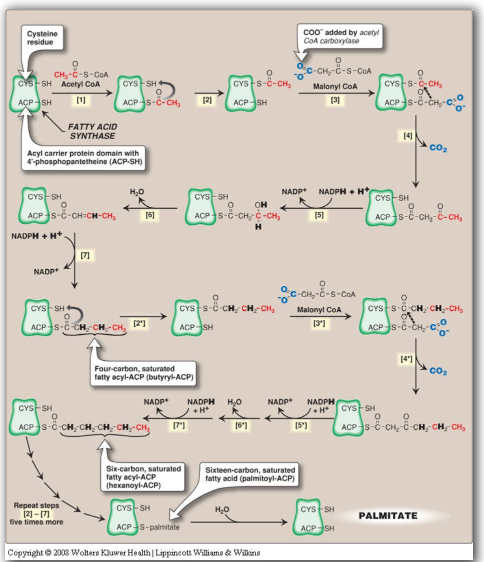
1. multifunctional enzyme with seven (7) different catalytic activities.
2. It is composed of a single polypeptide chain!
3. It has a special domain, the ACP, (acyl carrier protein) which covalently binds a 4'-phosphopantetheine molecule.



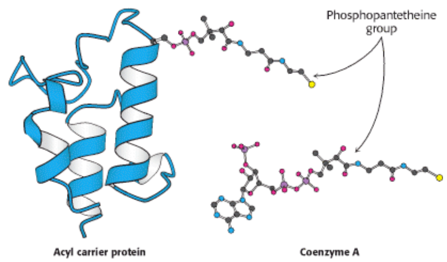

**Domain 1 [substrate entry]**
(1) acetyltransacylase
(2) malonyl CoA-ACP-transacylase
(3) 3-Ketoacyl-ACP synthase

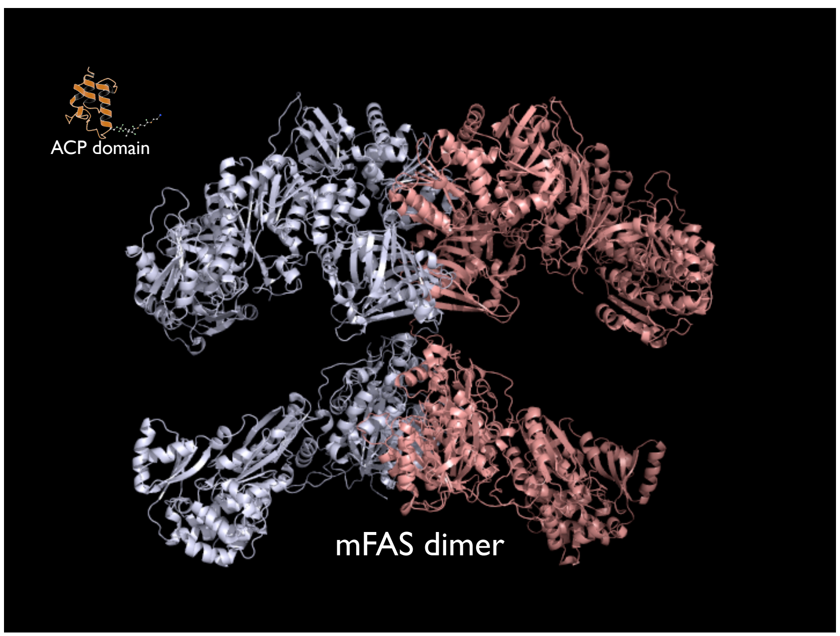
**Domain 2 [the reduction unit]**
(4) 3-Ketoacyl-ACP reductase
(5) 3-Hydroxyacyl-ACP dehydratase
(6) Enoyl-ACP reductase

**Domain 3 [the palmitate release unit]**
ACP (acyl carrier protein domain)
(7) Palmitoyl thioesterase

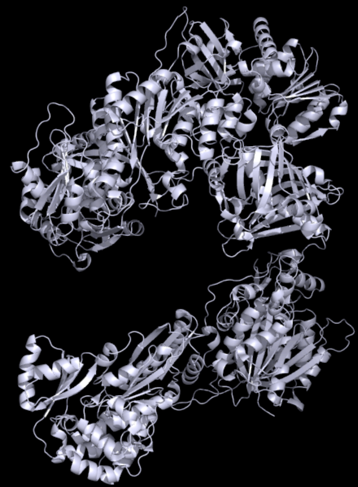


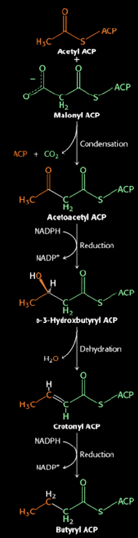
## Fatty acid synthase ACP domain with phosphopantetheine prosthetic group



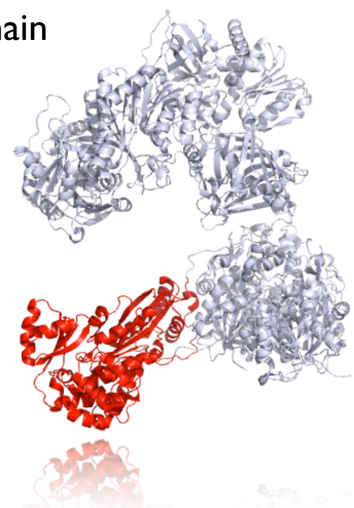
## (6) thioesterase {not shown}





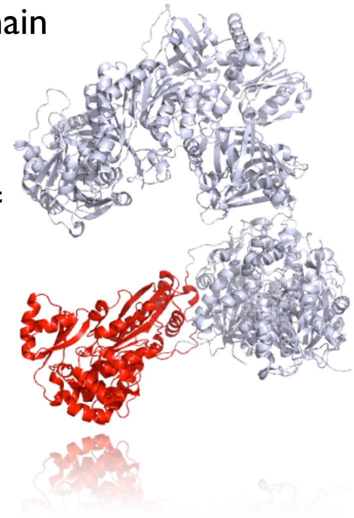

## malonyl transferase domain

1. transfers short chain acyl-CoA to ACP domain
2. uses both acetyl-CoA and malonyl-CoA with equal efficiency
3. can also utilize propionyl-CoA to form odd-length fatty acids



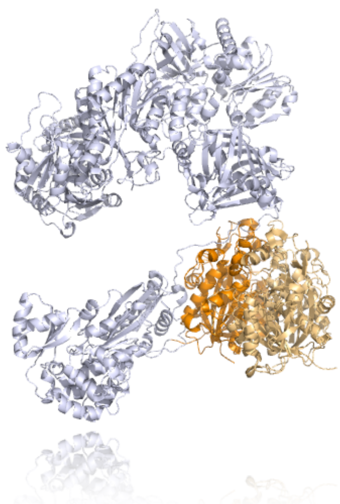
## malonyl transferase domain

**If malonyl transferase really can't distinguish between acetyl-CoA and malonyl-CoA, what happens if it binds and transfers several acetyl-CoA's in succession to ACP, instead of malonyl-CoA?**

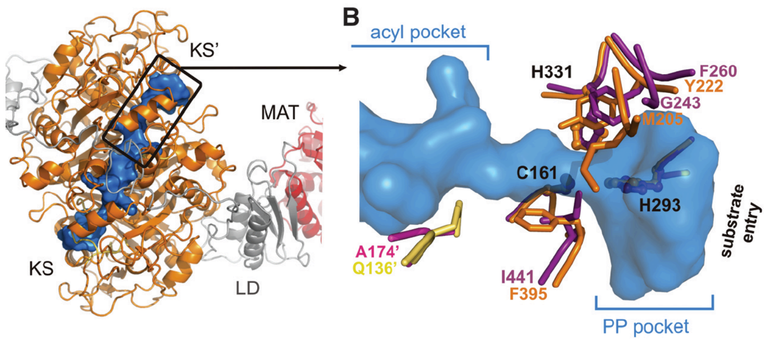


## 3-Ketoacyl-ACP-synthase

1. catalyzes the committed step in **acyl chain elongation**, but is not rate-limiting for **fatty acid synthesis** (acetyl CoA carboxylase)
2. somehow measures the growing chain and terminates elongation at 16 carbons.



# The deep pocket within ketoacyl synthase, in combination with thioesterase, are postulated to limit acyl chain length synthesis to 16 carbons




# Summary of fatty acid synthesis

**8 acetyl CoA + 14 NADPH + 14 H+ + 7 ATP**

**palmitic acid (16:0) + 8 CoA + 14 NADP⁺ + 7 ADP + 7 Pi + 7 H20**

1. The major suppliers of NADPH for fatty acid synthesis are:

   a) the hexose monophosphate shunt

   b) cytoplasmic malate dehydrogenase